Asymmetric synthesis of γ -aminophosphonates: The bio-isosteric analogs of γ -aminobutyric acid

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Abstract. The properties of aminophosphonates as transition state analogs of amino acids, and as antibacterial, antifungal and antiHIV agents attracted considerable attention in recent years. Although many reviews appeared in the literature covering α - and β -aminophosphonates, γ -aminophosphonates did not receive sufficient attention despite the fact that parent γ -aminophosphonic acid and its derivatives are bio-isosteric analogs of GABA (γ -amino butyric acid). This review provides a critical summary of the significance of γ -aminophosphonates and various approaches to their synthesis, with particular emphasis to asymmetric versions.

Keywords. γ -Aminophosphonic acid; γ -aminobutyric acid; isosteric analogs.

1. Introduction

Aminophosphonates mimic the tetrahedral transition states of amino acids, for instance, in enzyme mediated peptide bond hydrolysis. Further, the antibacterial, antifungal and antiHIV properties exhibited by aminophosphonates and the presence of aminophosphonate moiety in a natural product K-26 make them attractive synthetic targets.¹ γ -Aminophosphonic acids are bio-isosteric analogs of GABA (γ -amino butyric acid). The γ -aminophosphonic acid (GAPA) derivative Phaclofen **1a** is the first described GABA_B antagonist,² whereas parent γ -aminophosphonic acid (3-APPA) **2** is the partial agonist to GABA_B.³ Another GAPA derivative, fosmidomycin **3**, isolated from *Streptomyces lavendulae* shows strong antimalarial activity.⁴ A GAPA- α -aminocarboxylic acid hybrid, L-AP4 **4**, is known for its selective agonist activity towards metabotropic glutamate receptors mGluR2 and mGluR3 which in turn are involved in stimuli leading to neurodegenerative diseases (figure 1).⁵

The diverse biological activities of γ -aminophosphonic acids make them popular synthetic targets among organic chemists. As a consequence, there have been several reports of synthesis of racemic as well as enantioenriched γ -aminophosphonates over the last several years. An excellent review on β -hydroxy- γ -aminophosphonic acids has recently been published.⁶

α -Aminophosphonic acids⁷ and their β -analogs⁸ have also been extensively reviewed. Hence these subjects will not be covered in our discussion. This review will provide a concise view on synthetic strategies involved in incorporating key functional groups i.e., NH₂ and PO₃H at γ -position to each other. Description will comprise all reported methodologies emphasising on chiral pool, chiral auxiliary based and catalytic asymmetric synthesis of γ -aminophosphonic acid incorporated compounds, their derivatives and immediate precursors.

2. Racemic synthesis of γ -aminophosphonic acid and its derivatives

The first ever report of synthesis of γ -aminophosphonic acid was by Kosolapoff.⁹ γ -Aminophosphonic acid and its derivatives have always attracted attention of organic chemists and the synthetic efforts towards these molecules had started in the early 1950's with reports of racemic γ -aminophosphonic acid derivatives critically summarized by Chambers and Isbell in their report.¹⁰ A number of other reports followed thereafter.^{11–16} Racemic syntheses can be conveniently summarized using the type of methodology involved through various bond formations such as C–P, C–C and C–N bonds and a combination of these. Synthesis of racemic difluoroPhaclofen **1b** utilized C–C bond formation to incorporate the phosphonate ester group starting with 4-chloro- β -nitrostyrene **5a** (scheme 1).¹⁷ The role of propylene oxide in step 2 here (see also schemes 10, 13,

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Figure 1. Bioactive γ -aminophosphonic acids.

Scheme 1. Racemic synthesis of difluorinated phaclofen **1b**.

Scheme 2. Synthesis of 1-aminoalkanediphosphonic acid **11**.

Scheme 3. Johnson's approach to cyclopropyl analogs of 2-amino-4-phosphonobutanoic acid.

19 and **34**) is presumably to neutralize the hydrochloride salt formed upon acid hydrolysis of phosphonate ester and generate free phosphonic acid.

1-Aminoalkanediphosphonic acid **11** synthesis involves the incorporation of a γ -aminophosphonic acid as the key synthetic step. This step was implemented with phosphonate substituted propionaldehyde **7** as the starting material and phenylthiourea **9** as the source of nitrogen (scheme 2).¹⁸

A synthetic methodology using C–C bond formation by the reaction of 2-(diethoxyphosphinyl)acetaldehyde **16** and trimethyl *N*-(benzyloxycarbonyl)-phosphonoglycinate **12** was reported in the synthesis of cyclopropyl analogs of 2-amino-4-phosphonobutanoic acid (scheme 3).¹⁹

Another synthesis of phosphinothricine and other phosphorylic analogs of glutamic acid was reported

which started with phosphoric acid **20** followed by silylation using hexamethyldisilazide. The nitrogen functionality was introduced by a Michael reaction of diethyl acetamidomalonate **23** to the vinyl phosphonate **22** (scheme 4).²⁰

An example of application of Curtius reaction for introduction of nitrogen is presented in scheme 5.²¹

Scheme 4. Ragulin's approach to (±) AP4.

Cyclopentene carboxylate **25** was converted to Boc-protected amino intermediate **26** via a Curtius reaction. Intermediate **26** was hydroborated and oxidized to cyclopentanone intermediate **27** which was enolized and triflated to obtain intermediates **28** and **29**. The phosphonate was introduced by Pd catalysed coupling. The Pd-catalysed coupling of intermediates **28**

and **29** with diethylphosphite followed by hydrolysis of phosphonate resulted in the cyclic unsaturated γ -amino phosphonic acid derivatives **30** (scheme 5).

Another report of Curtius reaction as a method of introducing nitrogen in the structure is the racemic synthesis of γ -aminophosphonic acid **35** and α -hydroxy- γ -aminophosphonic acid derivatives as S1P receptor

Scheme 5. Synthesis of 1-amino-3-phosphono-3-cyclopentene-1-carboxylic acid **30**.

Scheme 6. Synthesis of potent S1P receptor agonists **35**.

Scheme 7. Synthesis of carbacycle bridged ($\pm$) AP4.

Scheme 8. Synthesis of γ -aminophosphonate **45** via aza-Michael addition to iminium phosphonate **43**.

antagonists (scheme 6).²² As a continuation of this research, racemic derivatives were synthesized with a nitrogen containing starting material and by introducing the phosphonate through a Wadsworth–Emmon's olefination. Enantiopure derivatives were also synthesized which will be described in the next section.

Johnson and co-workers have synthesized the racemic *trans*- and *cis*-isomers of 1-amino-2-phosphonomethyl-cyclobutanecarboxylic acid and cyclopentanecarboxylic acid **42** using Arbuzov chemistry for C–P bond formation followed by Strecker synthesis for adding the nitrogen at the γ -position (scheme 7).²³

Latest report on racemic synthesis of compounds belonging to this group is the synthesis of γ -amino- α -dehydroaminophosphonates **45** by an aza-Michael reaction of ammonia or other amines which is the source of incorporating nitrogen to an α , β -unsaturated iminium phosphonate (scheme 8).²⁴

3. Chiral pool synthesis of γ -aminophosphonic acid and derivatives

γ -Aminophosphonic acid derivatives are important precursors in the synthesis of biologically relevant molecules. It is a very well-established fact that medicinal chemistry works better with enantiopure compounds exhibiting a good biological profile and selectivity, rather than racemic mixtures.²⁵ The most conventional methods to make chirally pure intermediates is by chiral pool synthesis, i.e., starting with materials with one or more chiral centres with fixed stereochemistry and then retaining those through the remaining steps towards the target molecule. As ex-

pected, most reports on chiral pool synthesis presented here will be for making precursors to medically relevant compounds. Chiral pool synthesis can also incorporate the γ -aminophosphonyl group by forming C–P, C–C and C–N bonds using different reactions such as Arbuzov/Michaelis–Becker, radical addition, nucleophilic substitutions, olefination methodologies and their variations e.g., Horner–Wadsworth–Emmon's olefination, Curtius reaction, Michael addition and Diels–Alder reaction. The availability of different methodologies highlights the versatility of the chemistry involved.

3.1 γ -Aminophosphonylation through C–P bond formation

This section focuses on the synthetic routes for incorporating phosphonate functionality using starting materials with a nitrogen containing functional group. A general strategy is depicted in scheme 9. Protected γ -carboxy- γ -amino halides **46** are subjected to Michaelis–Becker or Arbuzov conditions to obtain phosphonated derivatives **47** which on acid hydrolysis give deprotected γ -aminophosphonic acid **4** (scheme 9).

(*S*)- α -MAP4 **52** was synthesized in good yield from *trans*-2-phenyloxazolidinone **48** by phosphonate incorporation using Michaelis–Becker reaction followed by acid hydrolysis (scheme 10).²⁶

1-Amino-2-phosphonomethylcyclopropanecarboxylic acids **56** were synthesized using Michaelis–Becker chemistry to incorporate the phosphonate group. The presence of cyclopropane ring in the substrate seemed to have considerable impact on the substitution reaction leading to the formation of ring cleaved by-products. Choice of protecting group on nitrogen in the substrate played an important role in the mechanism of ring cleavage. Trifluoroacetyl protecting group was found to be more favourable over conventional Boc protection in reducing the number of ring cleaved products thus increasing the yield. Boc group was removed from $\pm(1S, 2R)$ -1-(*tert*-butoxycarbonylamino)-2-bromomethyl cyclopropane-1-carboxylate **53** and the resulting amine was protected with trifluoromethyl

Scheme 9. General method for synthesis of γ -aminophosphonic acid via C–P bond formation.

acetyl group to obtain intermediate **54** which on treatment with trimethylphosphite yielded the phosphonate **55** with only the alkene side product **57**. Intermediate **55** was deprotected to obtain the required phosphonate derivative **56** as a zwitterion (scheme 11).²⁷

Another method belonging to this category is P–C bond formation via radical addition reaction. A unique method of introducing the phosphonate group at the γ -position is using inorganic white phosphorus.²⁸ L-Glutamic acid **58** was protected as an oxazolidinone to obtain intermediate **59**. The intermediate **59** was converted to a pyridine thione intermediate **60** followed by radical reaction with phosphorus, oxidation and deprotection gave the L-AP4 **4** (scheme 12).

In 1992, Zeiss had reported the synthesis of enantiopure L-phosphinothricin **65**, a natural amino acid which possesses antibiotic and herbicidal properties, via regioselective radical addition of alkyl methylphosphinate **63** to L-vinylglycine derivative **62** (scheme 13).²⁹

Radical reactions can be carried out successfully using hypophosphites. In this methodology, β , γ -unsaturated carbamate derivatives **62** were reacted with hypophosphites in the presence of a radical initiator under oxidative conditions to form the C–P bond as in intermediates **66** and **67**. Deprotection or further functionalization of **66** afforded the γ -aminophosphonic acid **4** and its derivatives. Precursors to Folypoly- γ -glutamate synthetase inhibitors were synthesized using

Scheme 10. Ma's approach toward synthesis of (S)-MAP4 **52**.

Scheme 11. Acher's synthesis of enantiopure APCPr **56**.

Scheme 12. Synthesis of enantiopure L-AP4 **4**.

$\text{NH}_4\text{H}_2\text{PO}_2$, Et_3B and air for initiating the radical reaction.³⁰ Acher and co-workers have used H_3PO_2 and AIBN in their synthetic scheme to obtain phosphinic acid **67** which was oxidized to phosphonic acid derivative **66** using DMSO and catalytic amount of iodine. This methodology contributed to developing a cost-effective synthesis of L-AP4 **4**.³¹ Liu *et al.* have used $\text{NH}_4\text{H}_2\text{PO}_2$ and Et_3B effectively to accomplish their synthesis of P-methylase substrates *N*-AcDMPT **68** and *N*-AcDMPTT **69** both incorporating the γ -aminophosphonic acid scaffold (scheme 14).³²

C–P bond formation can take place by nucleophilic phosphite addition reactions to carbonyl compounds. A representative example is presented in scheme 15. Chirally pure *N*-Boc *t*-butyl aspartate **70** was converted to the corresponding γ -phosphonate by phosphite addi-

tion using trimethylsilyl methyl phosphonate.³³ The hydroxyl group in intermediate **71** was removed by radical deoxygenation to obtain intermediate **72** which was transformed to TFA salt of L-AP4 **4**. Similar approach has been applied to obtain phosphoserine analogs.³⁴

3.2 γ -Aminophosphonylation through C–N bond formation

This strategy involves use of phosphonate incorporated starting material and synthetic methods of adding nitrogen functionality at the γ -position via C–N bond formation. Enantiopure **74** was subjected to Curtius rearrangement for the incorporation of nitrogen as a protected amine **75**. The intermediate was further

Scheme 13. Synthesis of enantiopure L-phosphinothricin **65**.

Scheme 14. Radical mediated synthesis of γ -aminophosphonic acid.

Scheme 15. Synthesis of phosphoserine analog **73**.

Scheme 16. Synthesis of L-AP4 via C–N bond formation.

oxidized to derivative **76** and the resulting deprotections gave L-AP4 **4** (scheme 16).³⁵

An interesting application of organometallic Pd catalysed addition of amines and other nucleophiles to the formation of γ -aminophosphonates has been reported by Spilling and co-workers.³⁶ They have shown that carbonates of allylic hydroxy phosphonates **77** underwent rearrangement with migration of double bond in conjugation to the phosphonate group to furnish α , β -unsaturated phosphonate derivatives **78**. This methodology was optimized and used for the synthesis of enantiomerically pure pyrrolidines. Vinyl tosylcarbamates **79** and trichloroacetimidates **81** also exhibited similar rearrangements (scheme 17).³⁶

3.3 γ -Aminophosphonylation through C–C bond formation

One of the reported methods of introducing a phosphonate group in nitrogen containing starting material is through C–C bond formation. A general scheme for the olefination approach is shown in

Scheme 17. γ -Aminophosphonate synthesis via allylic substitution.

scheme 18. This synthetic route involves olefination of α -aminocarboxaldehyde **83** under Horner–Wadsworth–Emmons conditions or its variations using *tetra*-alkyl methylene diphosphonates **84** and *n*-BuLi to afford the α , β -unsaturated- γ -amino phosphonates **85**. The alkene obtained can be converted to its saturated intermediate **86** by hydrogenation followed by removal of all protecting groups to obtain γ -aminophosphonic acid derivatives **87**.

Conformationally constrained analogs of (*R*)-2-amino-7-phosphonoheptanoic acid **91** by incorporating a functionalized pyrrolidine ring were synthesized by Langlois and co-workers using the above approach. The olefination in this synthesis using (2*R*, 5*S*)-2-cyano-5-formyl-1-methoxycarbonyl-pyrrolidine **88** to intermediate **89** was stereospecific affording only the *E*-stereoisomer which was then hydrogenated and deprotected to afford the constrained analog of the γ -aminophosphonic acid **91** (scheme 19).³⁷ The chemoselective

Scheme 18. General methods for synthesis of γ -aminophosphonates via C–C bond formation. Scheme 19. Synthesis of constrained γ -aminophosphonic acid **91**.

reaction of phosphonate with the aldehyde group as opposed to the nitrile in **88** is noteworthy.

The concise and stereocontrolled syntheses of phosphonate C-glycoside analogs of β -D-ManNAc and β -D-GlcNAc 1-O-phosphates reported by Wen and Hultin used a synthetic strategy comprising an olefination step.³⁸ This olefination had a variation where ZnBr_2 was used along with Li salt of *tetra*-alkylmethylene-diphosphonates to prevent retro-aldol/Wittig products. The products isolated were the thermodynamically favoured β -conformers. Interestingly, the olefination step was indirectly responsible for the β -stereoselectivity. Chiral *R* and *S*-phosphonoserines were synthesized efficiently using the Wadsworth–Emmons olefination method starting with Garner’s aldehyde obtained from L-serine or D-serine by Macdonald and co-workers.³⁹ This synthetic scheme traced the route outlined in the general scheme. More recently, Hogenauer *et al.* have synthesized FTY720 phosphate mimics comprising a γ -aminophosphonic acid scaffold using Horner–Wadsworth–Emmons olefination as the key step.⁴⁰

Closely related to the olefination strategy is the formation of C–C bond by nucleophilic attack of the Li salt of dialkyl methylphosphonate on α -amino carboxaldehyde. One commonly used chirally pure α -amino carboxaldehyde in literature is Garner’s aldehyde and its derivatives.

As shown in scheme 20, Garner’s aldehyde derivative **92** is reacted with the anion formed by reac-

tion of *n*-BuLi and dialkyl difluoromethylene phosphonate to obtain alcohol intermediate **93**. Depending on the target derivative the hydroxyl group may be removed using Martin’s deoxygenation method to give **94**. Further, acid hydrolysis removed the acetonide protection to give second alcohol intermediate **96** which was oxidized to acid or aldehyde **97**. Otaka and co-workers have successfully synthesized *N*-Boc-L-2-amino-4-(diethylphosphono)-4,4-difluorobutanoic acid by applying this chemistry.⁴¹ Yokomatsu *et al.* have applied this methodology to phenyl derivative of **92** to synthesize non-competitive inhibitors of sphingomyelinases.⁴² The successful application of this synthesis to obtain a phosphonothioate analogue by treating derivative of intermediate **94** with Lawesson’s reagent was reported in the diastereoselective synthesis of γ -amino- δ -hydroxy- α,α -difluorophosphonates (scheme 20).⁴³

β -oxo- γ -aminophosphonic acid derivatives may be regarded as a subclass of γ -aminophosphonic acid and are known to be the precursors or target molecules among medicinally relevant compounds. They can be synthesized by slightly modifying the reagents and conditions. Enantiomerically pure α -amino-carboxylic acid derivative **98** was subjected to nucleophilic attack by the Li salt of dimethyl methylene phosphonate to give protected derivatives **99** which when Boc-protected were deprotected using TMSBr in MeOH to afford the γ -amino-oxoalkyl derivatives **100** (scheme 21).

This strategy was applied in the synthesis of phosphonyl analogs of nucleotides by Natchev.⁴⁴ A

Scheme 20. Garner’s aldehyde **92** as chiral source for synthesis of γ -amino- α,α -difluorophosphonates.

Scheme 21. Synthesis of β -oxo- γ -aminophosphonic acid **100**.

synthesis of (3-amino-2-oxoalkyl)phosphonic acid in 95% ee as novel inhibitors of D-alanine:D-alanine ligase was reported by Chakravarty and co-workers.⁴⁵ Ordonez and co-workers have applied this strategy in their synthesis of 3-amino-2-ketophosphonates **100** ($R^2 = \text{Me, Bn}$; Pg = Bn).⁴⁶

A minor variation to formation of Li salt is that of anion formation using bases like EtONa. Alkylation of acylamino substituted malonates **102** with bromoethylene phosphonates **101** followed by hydrolysis of the ester and incorporation of thiol group was reported by Roques and co-workers thus making a chiral pure compound with thiol, amino and phosphonate functionalities in the same molecule (scheme 22).⁴⁷

A different methodology of forming γ -aminophosphonic acid derivatives through C–C bond formation and to the best of our knowledge the only one reported is using Friedel–Crafts reaction, as has been reported by Hale *et al.* in their synthesis of α -hydroxy- γ -aminophosphonic acid derivatives.⁴⁸ In this example, Friedel–Crafts acylation of alkyl benzene derivative **105** with enantiopure (*R*)-2-trifluoroacetylamido succinic anhydride **106** using AlCl_3 and subsequent conversion of CO to CH_2 followed by protection of the resulting

amine with Boc group afforded intermediate **107**. Intermediate **107** underwent a one carbon homologation via an Arndt–Eistert rearrangement, reduction to alcohol and Swern oxidation to aldehyde **108**. Pudovik reaction on aldehyde **108** afforded **109** as diastereomeric mixture which when subjected to separation yielded γ -aminophosphonic acid **110** as the major diastereomer (scheme 23).

3.4 γ -Aminophosphonylation through C–N and C–C bond formation

Substrates not comprising phosphonate or nitrogen containing functionality may have to be maneuvered to obtain γ -aminophosphonic acid scaffold. This section discusses methodologies to incorporate both the NH_2 and PO_3H groups using C–N and C–C bond formation.

As shown in scheme 24, diol **111** goes through azidation via Mitsunobu reaction with TMSN_3 as the azidation reagent to give azide intermediate **112**. After the introduction of nitrogen, reduction to amine and protection with benzyl group, alcohol is oxidized to aldehyde to carry out Emmons–Wadsworth olefination for incorporation of phosphonate group resulting in intermediate

Scheme 22. Roques's approach to δ -thiol- γ -aminophosphonate **104**.

Scheme 23. Synthesis of γ -aminophosphonate **110** using Friedel–Crafts reaction.

113. Deprotection and hydrolysis of phosphonate ester to acid yields the γ -aminophosphonic acid **114**.⁴⁹

Schmidt and co-workers have reported another similar manipulation to materialize the synthesis of homosphingosine-1-phosphonate. They have used azide **116** which was obtained by a Mitsunobu reaction on **115** as an intermediate for introducing nitrogen. The azide intermediate was debenzylated, azide reduced to amine which was protected with trifluoroacetyl group. Protection of terminal hydroxyl group using TBDMS afforded intermediate **117**. This was then converted to intermediate **118** through hydrolysis and coupling reaction with CDI. The TBDMS group was removed and the resulting hydroxyl was bromi-

nated using LiBr after mesylation to furnish bromo intermediate **119** which was phosphonated using Arbuzov reaction followed by hydrolysis to obtain the γ -aminophosphonic acid derivative/homosphingosine-1-phosphonate **120** (scheme 25).⁵⁰

An alternative approach involving nucleophilic attack for formation of C–N bond involves an S_N^2 substitution mechanism. Two reports using this route to γ -aminophosphonylation have been published.^{39,51} As shown in scheme 26, the attack is on a substituted oxirane ring **121** using the Li salt of diethyl methylene phosphonate resulting in the opening up of the oxirane ring to alcohol **122**. The alcohol is converted to an azide via a Mitsunobu reaction using DPPA, DIAD

Scheme 24. Bittman's approach to L-lyxo-phytosphingosine 1-phosphonate **114**.

Scheme 25. Schmidt's approach to homosphingosine-1-phosphonate **120**.

Scheme 26. Synthesis of γ -aminophosphonate via opening of oxiranes.

and polymer-based PPh_3 followed by reduction and conversion to Boc-protected intermediate **123**.³⁹

Alternatively, converting the OH group to a good leaving group such as OM and then performing an azidation using NaN_3/DMF in the presence of 18-crown-6 results in an azide intermediate which is reduced and protected to yield Boc-protected intermediate **123**.⁵¹ Deprotection of the Boc group and hydrolysis of phosphonate using TMSBr ⁵¹ or oxidation³⁹ of the alkyl group on intermediate **123** results in γ -aminophosphonate derivatives **124** and **125**, respectively. The epoxide **121** was used in enantiopure form in these reactions and the stereochemistry of the asymmetric centre was determined taking into account the reversal of the configuration after S_{N}^2 substitution by the azide nucleophile. Synthetic strategy was efficient as indicated by the good yields and clever application of chiral pool synthesis to obtain enantiomerically pure product.

3.5 γ -Aminophosphonylation through C–N and C–P bond formation

This section deals with synthesis of γ -aminophosphonates where both C–N and C–P bonds are not present in the starting material and are incorporated during the course of synthesis to obtain the γ -aminophosphonic acid derivatives.

A related application of this strategy has been used in the chiral pool synthesis of tamiphosphor **131**. As can be seen from the structure, tamiphosphor incorporates a γ -aminophosphonic acid scaffold. The strategy involves the formation of the C–N bond starting with intermediate **126** first being converted to azide **127** using Mitsunobu reaction or Boc protected amino derivative **129** using DDQ and tetrabutylammonium isocyanate as the source of amine followed by addition of *t*-BuOH. Both **127** and **129** were phosphonated using Pd catalysed coupling to obtain intermediates **128** and **130**. Both **128** and **130** on reduction and deprotection, respectively yielded tamiphosphor **131**. All intermediates and products were obtained in good yields (scheme 27).⁵²

3.6 γ -Aminophosphonylation through pericyclic reactions/rearrangements

A convenient approach to cyclic γ -aminophosphonic acid is through Diels–Alder reaction. Few reports on application of Diels–Alder reaction to synthesize of γ -aminophosphonic acid derivatives are presented in this section.

In the first example, ethyl propiolate **132** was phosphonated to an alkene derivative which underwent Diels–Alder reaction with sulpholene **133** to obtain cyclic ester **134** which was converted to

Scheme 27. Incorporation of amino and phosphonate groups for synthesis of tamiphosphor.

Scheme 28. Synthesis of cyclic γ -aminophosphonate **138** via Diels–Alder reaction.

Scheme 29. Synthesis of cyclic γ -aminophosphonate **141** via Diels–Alder reaction.

cyclopentanone derivative **135** by oxidation followed by decarboxylative rearrangement. This was then converted to hydantoin **136** and **137** by Bucherer–Bergs reaction which on hydrolysis with acids provided the respective cyclic γ -aminophosphonic acids, e.g., **138** (scheme 28).⁵³

Formation of hexacyclic ring structure alongside placing the N-containing (amido) functionality at γ -position to the phosphonate group by Diels–Alder reaction was explored by Marchand–Brynaert *et al.*⁵⁴ They have used chiral aminodiene such as *N*-dienyl-L-

pyroglutamate **139** and β -acetyl vinyl phosphonate **140** in toluene under reflux conditions to obtain cyclohexene adduct **141** with excellent regioselectivity and good diastereoselectivity (scheme 29).

The utility of this reaction exists in further functionalization, an example of which is reduction of the amide to amine which may provide the γ -aminophosphonic acid.

Recently, the target γ -aminophosphonic acid scaffold was achieved via an alkylation–dearomatization–rearrangement reaction. In this novel protocol, *bis*(*N*-benzyl-*N*-methyl)-*p*-arylphosphonic diamide **142** was deprotonated using *s*-BuLi and the resulting intermediate **144** was trapped with electrophiles to obtain single or mixtures of dearomatized products **146**, **147** and **148** subject to the electrophile involved. The products are separable by chromatography. The separated product, e.g., **146**, is hydrolysed to obtain functionalized *N*-(methyl)- γ -aminophosphonic acids **145** (scheme 30).⁵⁵

Scheme 30. Dearomatization–alkylation for the synthesis of γ -aminophosphonate **145**.

Scheme 31. Incorporation of amino functionality via Strecker reaction.

Scheme 32. Enantiopure sulphinamine **150** as chiral source of amine.

4. Chiral auxiliary facilitated synthesis of γ -aminophosphonic acids

Few examples involving the use of chiral auxiliaries have been reported for the synthesis of γ -aminophosphonic acids. These reactions involve the use of starting materials with a chirality inducing scaffold such as amino acid derivatives, bislactim ethers, oxazolidinone derivative or a sulphinic acid derivative which can be easily removed to obtain the target compounds. Among the earliest reports the use of chiral auxiliary is the use of (*S*)-(-)-2-methylbenzylamine. Here the (*S*)-(-)-2-methylbenzylamine is used to form an enantiopure Schiff's base with the aldehyde **7** followed by addition of HCN afforded **149** with 88% de. The hydrolysis of both cyano and phosphonate groups followed by debenzoylation results in L-AP4 **4** with 88% ee (scheme 31).⁵⁶

A novel approach to synthesize γ -aminophosphonic acid derivative **4** is the use of (+)-(*S*)-sulphinimine as reported by Mikołajczyk and co-worker.⁵⁷ In this synthesis, the phosphonate was incorporated through formation of an enantiopure imine **151** from aldehyde **7** and enantiopure sulfoxamide **150** followed by addition of CN as nucleophile using Et_2AlCN . The addition of the nucleophile to enantiopure imine **151** resulted **152** in 9:1 diastereomeric ratio which upon hydrolysis gave aminophosphonic acid **4** in good yield (scheme 32).⁵⁷

Another report involved the use of Michael addition of chiral Schiff bases to vinyl phosphorus compounds. The use of *t*-BuOK facilitated the Michael addition of

the anion formed from Schiff base **153** to **22** followed by hydrolysis using 6 N HCl to obtain L-AP4 with 50% optical purity (scheme 33).⁵⁸

Closely followed the report of asymmetric synthesis of 2-amino-4-phosphonobutanoic acid **4** (L-AP4) by alkylation of Schiff base **157**. The chiral Schiff base **157** prepared by the reaction of (*S*)-*o*-[(*N*-benzylpropyl)-amino]benzophenone (BPB) **154** with Ni ions **156** and glycine **155** (scheme 34).⁵⁹

Michael addition reactions to facilitate C–P bond formation have been described in great detail in the asymmetric catalysis section of this review later. Diastereoselective addition of dialkyl phosphite **161** to α , β -unsaturated chiral amides **160** to form the C–P bond was published by Quirion and co-workers (scheme 35).⁶⁰ The highlight of this methodology was the efficient 1,5-asymmetric induction using chiral amino alcohols. The overall impact of different substituents in the phosphonate, C-5 and *N*-protections were investigated.

Thus α , β -unsaturated amide derivative **160** underwent Michael addition with different sodium dialkyl phosphonates **161** in THF at -20°C to obtain Michael adducts **162**. Excellent diastereoselectivities

Scheme 33. Enantiopure glycine Schiff base **153** as chiral source.

Scheme 34. *S*-proline-based Ni-Schiff base complex as chiral inducer.

Scheme 35. Synthesis of chiral aminophosphonates **163**.

were observed with aminobutyl alcohol, valinol and phenylglycinol derivatives of **160**. Olefinic substituents also had a considerable impact with alkyl substituents exhibiting better diastereoselectivities (de >90%) than their aryl counterparts. Incorporation of bulkier alkyl phosphonates such as diisopropyl phosphonates also had a better impact on diastereoselectivities. Among the *N*-protection, the benzyl protection seemed to retain good diastereoselectivities. The ultimate application of this strategy was the convenient reduction of the amides to the amines using BH_3 -THF to obtain γ -amino phosphonates **163** (scheme 35).⁶⁰

Michael addition condition has been used to form C–C bond to incorporate amino group at γ -position to phosphonate. Bislactim ether methodology owes its origin to Schöllkopf.⁶¹ Bislactim ether **164** has been used for Michael addition to obtain the precursors to spinghanine and sphingosine-1-phosphate analogs and this report also summarizes very well the later uses of bislactim ethers **164**.⁶² Ojea and co-workers have reported the methodologies where single enantiomer of Li salts of *cyclo*-[AlaD-Val] (Schöllkopf's bislactim ether) **164** was reacted with the α , β -unsaturated phosphonates **165** to give adducts

166.^{63–67} The treatments of the Michael adduct **166** with acid results in the amine intermediate **167** and the resulting ester incorporated intermediate is subjected to hydrolysis to respective acids **168**. This strategy has been used effectively in the enantiospecific synthesis of 2-amino-3-methyl-4-phosphonobutanoic acid using prop-2-enylphosphonates (de >95%) and C-1' (de >88%).^{63,64} This method demonstrated an excellent capability of inducing chirality with good diastereoselectivities at the newly formed chiral centres C-2. Yields were improved by using excess of bislactim ether which prevented the formation of 1:2 adducts which is fairly common in these types of reactions.

The same group further conducted experiments with different *E*-alkenylphosphonates **165** by varying substituents at R^2 position with groups such as *i*-Pr, Ph, CH_2OBn , CH_2NHCbz , and CHCH_2 . Phosphonates with alkyl substitutions gave better yield for the product as compared to the aryl substituents. 2,5-*Trans*-2,1'-anti adducts were obtained with a de >85% over other diastereomers. High diastereoselectivities were attributed to the favourable steric and electronic effects of the tetrahedral phosphoryl group (scheme 36).^{65,66} Ojea *et al.* have established that adducts obtained by

using Bislactim ether **164** and substituted vinyl phosphonates **165** can also be obtained by electrophilic substitution on the bislactim ether derivative of *cyclo*-[L-AP4-D-Val] **169**.⁶⁷ Thus an alternative methodology to making α -substituted- γ -aminophosphonic acid derivatives using C–C bond formation was reported. The bislactim ether **169** was reacted with LDA in THF at -78°C to form the carbanion stabilized by the phosphonate ester which attacked the electrophile to form the substituted phosphonate **170** with 1:1 to 3:1 diastereomeric ratios (scheme 37).^{67,68}

Further functionalization of **169** using CF_3 , N_3 and olefin substituents was explored. Olefination at α -carbon of phosphonate group of **171** was performed using the Peterson or tin-Peterson olefination approach. The functionalized bislactim derivative could be hydrolysed to obtain the substituted γ -aminophosphonate derivatives **173** (scheme 38).^{68,69}

An enantioselective synthesis of (*R*)-AP4 was reported using hexahydrobenzooxazolidinone **174** as a chiral auxiliary. This synthesis involved acylation of nitro-

gen of the chiral auxiliary with (diethoxy-phosphoryl) propionyl chloride **175** followed by a diastereoselective azidation to obtain azide **176**. Removal of the chiral auxiliary followed by catalytic hydrogenation and hydrolysis afforded (*R*)-AP4 **4** (scheme 39).⁷⁰

Preliminary achiral synthesis of phosphonocyclopentene amino acids were reported from Pellicciari group.²¹ Further using the chiral auxiliary approach two new cyclopropyl glycine analogs were reported from the same group.⁷¹ Detailed synthesis using this chiral auxiliary approach and incorporation of phenyl group on the cyclopropyl glycine core structure led to phenylphosphonocyclopropyl glycine (PPCG) analogs.⁷² To synthesize the PCG-1, PCG-2, PPCG-3 and PPCG-4, Pellicciari group started with racemic epoxyphosphonate **177** which gave the cyclopropanated aldehyde **178** via ring opening of epoxy functional group followed by oxidation of alcohol. Separable major (2*S*) diastereomeric mixture of amines **179** and **180** along with minor (2*R*) diastereomers (2*S*:2*R* = 50:25) was obtained via Strecker reaction of

Scheme 36. Michael addition of bislactim **164** to vinyl phosphonates **165**.

Scheme 37. Base mediated α -functionalization of phosphonate **169**.

Scheme 38. α -Functionalization of phosphonate via Peterson or tin-Peterson olefination.

aldehyde **178** using *R*-phenylglycinol as chiral amine. Then removal of chiral auxiliary, hydrolysis of phosphonate and cyano group to corresponding acid gave the PCG and PPCG derivatives (scheme 40).^{71,72}

For PPCG **1** and **2** they started with the reaction of anion of α -chloro-isopropyl-phosphonate with *E*-tert-butylcinnamate **183** to obtain mixture of diastereoisomers of which **184** and **185** were separated. Diastereomer

Scheme 39. Synthesis of (*R*)-AP4 via diastereoselective azidation.

Scheme 40. Enantioselective synthesis of cyclic analogs of AP4.

Scheme 41. Enantioselective synthesis of PPCG derivatives **188** and **190**.

184 was converted to aldehyde **186** as a mixture of diastereoisomers. Introduction of chiral auxiliary followed by CN group yielded two separable major (*2S*) diastereoisomers **187** and **189** along with two minor (*2R*) diastereoisomers in 85:15 ratio. The two major diastereoisomers **187** and **189** were converted to PPCG-1 and PPCG-2, respectively, by removing chiral auxiliary and hydrolysis of cyano as well as phosphonate group (scheme 41).⁷²

5. Catalytic asymmetric synthesis of γ -aminophosphonates

Catalytic asymmetric synthesis has been a topic of great interest mainly due to easy availability and low loading of chiral catalyst that make the process more economical. Very few methods for catalytic asymmetric synthesis of γ -aminophosphonic acids have appeared in literature. Just as has been described for chiral pool synthesis, the catalytic methods, classified depending upon the types of bonds formed in the reactions, namely, C–P, C–N and C–C Michael additions, appear to be the most

convenient ones, especially for generating an asymmetric centre. However, a report on enantioselective synthesis of Phaclofen which involves catalytic asymmetric hydrogenation appears as an exception.

5.1 Catalytic asymmetric phosphorylation

Several catalytic systems have been reported for synthesis of α - and β -aminophosphonates.^{7,8,73} In contrast, there are only few reports available for synthesis of enantioenriched γ -aminophosphonates. In 2007, Jørgensen group reported catalytic asymmetric synthesis of γ -aminophosphonate via 1,4-addition of trialkylphosphite to α , β -unsaturated aldehydes **191** followed by reductive amination for the first time (scheme 42).⁷⁴

The Michael addition was efficiently catalysed by diarylprolinol derivative **C1** in the presence of benzoic acid and sodium iodide albeit in poor yields and moderate enantioselectivity. Among the trialkylphosphites, bulky tri-*iso*-propyl phosphite provided the best yield and enantioselectivity. The better chemoselectivity in Michael addition was achieved by lowering the LUMO

Scheme 42. γ -Aminophosphonate synthesis via β -phosphonylation of α , β -unsaturated aldehydes **191**.

Scheme 43. Wang's approach to γ -aminophosphonate **198**.

of α , β -unsaturated carbonyl compound **191** via formation of iminium ion intermediate **TS1**. The bulky substituent on chiral pyrrolidine block the *Re* face of the *in situ* generated iminium ion intermediate and thus trialkyl phosphite approaches from *Si* face to give Michael adducts with *S* configuration (when R^1 is aryl). Further these Michael adducts **192** were converted into γ -aminophosphonates **193** and **194** via Strecker reaction and reductive amination, respectively (scheme 42).⁷⁴

In another approach, Wang group has disclosed the first highly enantioselective Michael addition of dialkyl and diarylphosphites **195** to α , β -unsaturated *N*-acylpyrroles **196** catalysed by dinuclear zinc complex of catalyst **C2** (scheme 43).⁷⁵ Especially, diethyl phosphite with broad spectrum of α , β -unsaturated *N*-acylpyrroles **196** provided almost optically pure amidophosphonates **197** with excellent yield. The utility of this Michael addition protocol was demonstrated by synthesizing enantioenriched γ -aminophosphonate **198** from amido-phosphonate **197** using simple chemical transformation.

5.2 Phosphonylation involving catalytic asymmetric hydrogenation

Earlier reports on synthesis of Phaclofen involved a racemic synthesis and usage of methods of resolution to obtain the *R*-enantiomer.⁷⁶ Recently, Duan *et al.* have reported the first enantioselective synthesis of (*R*)-Phaclofen **1** via a Rh catalysed asymmetric hydrogenation with a P-stereogenic Bophoz type phosphine–

aminophosphine ligand.²⁵ Thus, the bromide **199** is phosphonated using Arbuzov conditions to obtain intermediate **200** which was hydrogenated using **C3** as a ligand with 93–97% ee. Hydrolysis of the ester **201** followed by treatment with NaN_3 resulted in the γ -aminophosphonic acid derivative (*R*)-Phaclofen **1** with 96% ee (scheme 44).

6. γ -Nitrophosphonates via Michael addition of phosphonates to nitroalkenes

This review will not be completed without a brief discussion on γ -nitrophosphonates which are the immediate precursors to γ -aminophosphonates. γ -Nitrophosphonates may be considered as potential precursors to γ -aminophosphonates. However, they have been explored very sparingly with sporadic reports of synthesis incorporating a γ -nitrophosphonate scaffold.^{77–85} As a research group, we have been pursuing nitroalkene chemistry with great interest realizing the immense application potential of γ -nitrophosphonates. Our group has developed an efficient method for synthesis of γ -nitrophosphonates **203** via diastereo- and enantioselective Michael addition of α -lithiated alkyl phosphonates **202** to a variety of aromatic nitroalkenes **5**.⁸⁶ The reaction catalysed by 50 mol% of cinchonine **C4** in the presence of 3 equivalent of LDA proceeded very smoothly and provided the products in high yields, diastereo- and enantioselectivities in most cases (scheme 45). The stereochemical outcome of the Michael adduct **203** was rationalized in terms **TS2**.

Scheme 44. Enantioselective synthesis of (*R*)-Phaclofen **1**.

Scheme 45. Approaches to γ -aminophosphonates via Michael addition of phosphonates to nitroalkenes.

Scheme 46. Effect of achiral additives on diastereo- and enantioselectivities.

Both nitroalkene **5** and alkyl phosphonate **202** coordinate to lithium centre of lithiated-cinchonine to form a tetracoordinated transition state **TS2**. Then the phosphonate **202** adds in a Michael fashion from the *Re*, *Si* face to nitroalkene **5** to afford the γ -nitrophosphonate **203** with *R*, *R* configuration.

The most interesting and useful aspect of this catalyst system is reversal in enantioselectivity of γ -nitrophosphonates **203a** with same chiral source in the presence of different achiral additives (scheme 46).⁸⁷ The addition of achiral additives such as TMEDA, HMPA, ethylenediamine, ethylene glycol and 12-crown-4 with cinchonine-Li precatalyst retained the stereoselectivity (*R*,*R*-major isomer) with decrease in yields whereas the addition of NMM, DMAP and diethyl ether caused a reversal of enantioselectivity (*S*,*S*-major isomer) without affecting the diastereoselectivity and yield. More importantly, both the enantiomers (*R*,*R*) and (*S*,*S*) could be synthesized with absolute enantioselectivity using two different solvents, THF and diethyl ether, respectively.

Another report on the synthesis of γ -nitrophosphonates using chiral thiourea based cinchonine catalyst appeared recently which involved asymmetric Michael addition of β -oxo phosphonates **204** to nitroalkenes **5** (scheme 47).⁸⁸ Optimized yields were reported to be in the range of 81–87%. The reactions exhibited moderate diastereoselectivity with good

enantiomeric excesses in case of bulkier and polar aryl substituents such as 1-naphthyl and 2-methoxyphenyl.

Very recently, Mukherjee and co-workers have developed an enantio- and diastereoselective Michael addition of α -substituted nitrophosphonates **206** to nitroalkenes **5** to synthesize α , γ -dinitro phosphonates **207** (scheme 48).⁸⁹ Though various aryl and heteroaryl nitroalkenes provided the desired adducts with moderate to good selectivities, aliphatic nitroalkenes were particularly excellent substrates for this reaction and provided the adducts up to 20:1 diastereomeric ratio with absolute enantioselectivity. Further, the synthetic utility of this method was demonstrated by the synthesis of enantioenriched pyrazolidin-3-ylphosphonate **208** via reductive N–N bond formation.

7. γ -Aminophosphonates via Michael addition of glycine equivalents to ethylidenebisphosphonates

Considering the biological and chemical importance of *gem*-bisphosphonates and γ -aminophosphonates, in 2009, Shibasaki group reported *S*-BINAM derived dinuclear Ni₂-schiff base **C7** mediated asymmetric Michael addition of nitroacetates **210** to ethylidenebisphosphonates **209** to afford the Michael adduct **211** in moderate to good yields and enantioselectivity (scheme 49).⁹⁰ The Michael adduct **211** was converted into corresponding γ -aminophosphonate **212** via reduction of nitro group using NiCl₂ and NaBH₄.

Recently, Wang group reported a highly diastereo- and enantioselective synthesis of γ -amino-*gem*-bisphosphonates **215** (scheme 50).⁹¹ The reaction was efficiently catalysed by (*S*)-TF-BiphamPhos **C8**-CuBF₄ complex affording Michael adduct **215** in good yields, diastereo- and enantioselectivities. These reaction conditions are tolerant to several functional groups and they provided a broad spectrum of substrate scope. The high

Scheme 47. Michael addition of β -keto phosphonate **204** to nitroalkenes **5**.

diastereo- and enantioselectivities were explained in terms of **TS3**. The active nucleophile azomethine ylide **214** coordinates with copper of active catalyst (*S*)-TF-BiphamPhos **C8**-Cu complex to form catalytically

active tetracoordinated complex **TS3**. The high steric crowding created by phenyl ring attached to phosphorous atom of chiral ligand prevents the approach of alkylidene bisphosphates **213** from bottom face of

Scheme 48. Enantioselective synthesis of α, γ -dinitrophosphonates **207**.

Scheme 49. Shibasaki's approach towards γ -amino-*gem*-bisphosphonates **212**.

Scheme 50. Synthesis of densely substituted γ -amino-*gem*-bisphosphonates **211**.

coordinated azomethine ylide **214**. Thus, the favourable top face approach of alkylidene bisphosphates **213** to coordinated azomethine ylide affords γ -amino bisphosphonate **215** with 2*R*,3*S* configuration.

8. Conclusions

γ -Aminophosphonates and related compounds, due to their structural resemblance to glutamates, have immense therapeutic potential as glutamate receptor agonists and antagonists. Their multifaceted biological activities have contributed to enhancing interests in investigations in medicinal chemistry related to these compounds. As a result of this, the efforts towards newer methodologies for the synthesis of γ -aminophosphonates, their analogs and their precursors have gained momentum. Overall, the trend has been towards optimization and application of asymmetric synthesis to conveniently obtain enantiopure molecules for biological evaluation alongside studying the interesting synthetic methodologies and mechanisms involved. Catalytic asymmetric synthesis of these molecules is emerging as an attractive area of research. This review was our attempt to further highlight the increasing importance of γ -aminophosphonic acid derivatives by summarizing the different methodologies of syntheses available in literature.

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Abbreviations

APCPr	1-Amino-2-phosphonomethylcyclopropanecarboxylic acid
<i>N</i> -AcDMPT	<i>N</i> -Acetyldemethyl phosphinothricin
<i>N</i> -AcDMPTT	<i>N</i> -Acetyldemethyl phosphinothricin tripeptide
<i>S</i> -BINAM	(<i>S</i>)-(-)-1,1'-Binaphthalene-2,2'-diamine
CDI	1,1'-Carbonyldiimidazole
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate

DMAP	4-Dimethylaminopyridine
DMP	Dess–Martin periodinane
DMPU	<i>N,N'</i> -Dimethyl- <i>N,N'</i> -trimethyleurea
DPPA	Diphenylphosphoryl azide
GABA	γ -Aminobutyric acid
GAPA	γ -Aminophosphonic acid
HMPA	Hexamethylphosphoramide
LDA	Lithium di-isopropylamide
LiHMDS	Lithium hexamethyldisilazide
MPLC	Medium pressure liquid chromatography
NMM	<i>N</i> -Methylmorpholine
NaHMDS	Sodium hexamethyldisilazide
PCC	Pyridinium chlorochromate
PTSA	<i>p</i> -Toluene sulphonic acid
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>Tert</i> -butyldimethylsilyl
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMSBr	Trimethylsilyl bromide
TMSI	Trimethylsilyl iodide
TMSN ₃	Trimethylsilyl azide

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